

Null Results in Brief

No Association between Toenail Selenium Levels and Bladder Cancer Risk¹

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Introduction

Geographic variations in bladder cancer risk, observed in the United States and other countries, have been ecologically related to soil selenium levels. Evidence from clinical trials, observational, and animal studies suggests that selenium is anticarcinogenic and can affect the risk of developing cancer. Common malignancies, such as those of the lung, prostate, and colon, account largely for the reported associations between selenium and total cancer incidence, but with few data, little is known about the relation between selenium and other cancers. Two prospective epidemiologic studies reported elevated risk of bladder cancer among individuals with low serum concentrations of selenium (1, 2). No association was observed between selenium levels and bladder cancer risk in three studies, measuring serum (3) and toenails (4), and in a selenium trial (5). The number of bladder cancer cases in these five studies ranged between 8 and 35. We evaluated the association between toenail selenium concentrations and bladder cancer risk in a cohort of male smokers with 132 bladder cancer cases.

Methods

The α -Tocopherol, β -Carotene Cancer Prevention Study was established between 1985 and 1988 when 29,133 male smokers ages 50–69 years living in southwestern Finland agreed to participate. The study was a randomized, double-blinded, placebo-controlled prevention trial to test the effect of α -tocopherol (50 mg) and β -carotene (20 mg) daily supplementation on lung cancer incidence using a 2×2 factorial design. At baseline, participants were measured for height and weight, completed a demographic and general medical history questionnaire, along with a detailed self-administered dietary questionnaire, and provided toenails clippings. From baseline to the end of April 1993, 132 cases of bladder cancer were identified through the

Finnish Cancer Registry and the Register of Causes of Death. The study was approved by the Institutional Review Boards of both the National Public Health Institute in Finland and the National Cancer Institute in the United States.

One control was matched to each case based on: age (up to ± 5 years), intervention group, and date of toenail collection (± 15 days), to control for the influence of selenium soil fortification, which began in Finland in 1984. Toenail selenium concentrations were determined on 10–50 mg samples by acid-digestion fluorimetry using 2,3-diaminonaphthalene to produce the piaseleole. ORs³ and 95% CIs were estimated using conditional logistic regression models to adjust for other potential risk factors (not matched on), such as dose and duration of cigarette smoking.

Results

Most baseline characteristics, including body mass index (kg/m^2), intakes of total energy, percentage of calories from fat, and alcohol were similar for bladder cancer cases and controls. Cases had smoked cigarettes for 40 years compared with 38 years among controls. Toenail selenium levels increased substantially during the toenail collection period, with mean levels ranging from 0.41 $\mu\text{g}/\text{gram}$ in 1985 to 0.67 $\mu\text{g}/\text{gram}$ in 1988, because of soil fortification.

No association was observed between toenail selenium levels and risk of bladder cancer overall (OR = 0.87, 95% CI, 0.30–2.52, for highest *versus* lowest quartile of selenium level, adjusting for smoking dose and duration). Stratifying the data by year of toenail collection yielded similar results (Table 1). In addition to the overall analysis, where the cutpoints for the quartiles were based on the levels of all of the controls, we performed an analysis combining the tertile cutpoints for each of the respective years of toenail collection (Table 1). Other modeling techniques to account for changes in selenium levels over time (using residual methods) did not change the above results.

Discussion

We observed no association between toenail selenium concentrations and bladder cancer risk among male smokers. We had 86% power to detect a significant test of trend ($\alpha = 0.05$) given an OR of 2.5 in the top tertile for the lowest compared with the highest tertile. However, the power was lower to detect a significant test of trend given an OR of 2.0 in the top tertile (*i.e.*, 63%). Our results are based on the assumption that the ranking of participants based on selenium levels remained constant during follow-up. Therefore, we conclude that based on our findings, a strong relationship between selenium biochemical concentrations and bladder cancer risk is unlikely. Two studies examining serum levels of selenium and bladder cancer re-

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³ The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 1 ORs of bladder cancer by tertiles of selenium level stratifying by year of toenail collection and overall

	Tertiles of selenium			<i>P</i> trend test
	1	2	3	
Year 1 (1985)				
No. of cases/controls	6/6	7/6	6/7	
Median (μg/g)	0.340	0.391	0.453	
MV OR ^a	1.0	1.02	0.72	0.70
95% CI	referent	(0.16–6.67)	(0.10–5.26)	
Year 2 (1986)				
No. of cases/controls	14/16	17/14	15/16	
Median (μg/g)	0.408	0.493	0.593	
MV OR ^a	1.0	1.39	1.00	0.93
95% CI	referent	(0.50–3.88)	(0.29–3.46)	
Year 3 (1987)				
No. of cases/controls	11/9	10/10	9/11	
Median (μg/g)	0.525	0.593	0.704	
MV OR ^a	1.0	0.76	0.56	0.43
95% CI	referent	(0.19–3.03)	(0.14–2.33)	
Year 4 (1988)				
No. of cases/controls	13/12	13/13	12/13	
Median (μg/g)	0.580	0.642	0.746	
MV OR ^a	1.0	0.90	0.82	0.75
95% CI	referent	(0.28–2.86)	(0.25–2.70)	
Combined ^b				
No. of cases/controls	44/43	47/43	42/47	
MV OR ^a	1.0	0.88	0.90	0.79
95% CI	referent	(0.47–1.68)	(0.45–1.78)	

^a MV OR includes smoking dose and duration in addition to the matching factors (age, intervention group, and date of toenail collection).

^b Cutpoints for tertiles are different for each year.

ported relative risks of 2.1 (2) and 3.1 (1) for low compared with high serum levels; however, case numbers were very small (35 and 29, respectively). The major limitation of this study was that toenail selenium levels changed over time because of the national agricultural soil fortification that occurred during the period of toenail collection for this study. Therefore, we cannot exclude the possibility that bladder cancer risk may be elevated at selenium concentrations lower than those observed in this study.

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